



“applicant” for that foreign patent document.<sup>1</sup> The original form PTO-1449 submitted on September 1, 2006 was in total compliance with Rules 1.97 and 1.98, and did not include the *optional* “patentee” or “applicant” identification with respect to the listed “*Foreign Patent Documents*.”

The undersigned pointed out to the Examiner that Rule 1.98(b)(4) requires that *foreign* patents and *foreign* published application listed in an IDS “must be identified by the country or patent office which issued the patent or published the application, an appropriate document number, and the publication date indicated on the patent or published application.” There is no requirement that the patentee or applicant be listed for “Foreign Patent Documents.” The foreign patent document listings on the original September 1, 2006 form PTO-1449 included *all* of this information required by the Rule. The undersigned further pointed out to the Examiner that MPEP § 609, seven paragraphs after quoting Rule 1.98, states that “[o]nce the minimum requirements of 37 CFR 1.97 and 37 CFR 1.98 are met, *the examiner has an obligation to consider the information*” (emphasis added). Nevertheless, and as a courtesy to the Examiner, the undersigned agreed to resubmit the September 1, 2006 form PTO-1449 with an additional column under Foreign Patent Documents identifying the applicant on each of the listed foreign patent documents.

Examiner Truong also indicated to the undersigned in a telephone discussion earlier this week that she could not find a copy of eight of the listed Foreign Patent Documents in the internal Patent Office database, which she identified as document numbers 84, 88, 97, 99, 120, 126, 132 and 133 on the September 1, 2006 form PTO-1449. The undersigned has personally checked the US PTO PAIR electronic database for this application, and hereby personally verifies that an electronic copy of each of the published PCT applications corresponding to such document numbers 84, 88, 97, 99, 120, 126, 132 and 133 is present in the US PTO PAIR database for this application, and noted as having been received on September 1, 2006, except for the published PCT application corresponding to document #97 (WO 01/32651), which was listed in and filed with the form PTO-1449 filed with this application on March 15, 2006, and is present in the PAIR database as of that earlier date.

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<sup>1</sup> Any such requirement by “Publications” is not understood, since to date an issued patent does not include the name of the patentee or applicant in the listing of “Foreign Patent Documents” on the face of a granted patent.

To assist the Examiner in locating electronic copies of these eight documents in the PAIR database, attached to this Information Disclosure Statement is a 5-page printout of the "Image File Wrapper" from PAIR on which the undersigned has personally noted the location in that image file of each of the eight foreign patent documents, identified by both document number and the publication number of those published PCT applications. The Examiner will note that the right-hand column on this printout gives the number of pages of each document, which should assist in locating the electronic copy of each of the eight documents. Also attached to this printout is the front page of each of the eight documents in question *printed from this PAIR database*.

In view of all of the above, it is respectfully and *urgently* requested that the Examiner acknowledge consideration of each of the documents on the attached version of the September 1, 2006 PTO-1449 by placing her initials where indicated, and fax a copy of the initialed copy to the undersigned (fax number listed below) prior to the June 11, 2009 due date for the Issue Fee in this application, if at all possible.

If the Examiner has any questions with regard to this filing or any other matter concerning this Application, it is respectfully requested that the Examiner telephone the undersigned at the number listed below.

Inasmuch as this is a courtesy resubmission of a previously submitted form PTO-1449 that was in full compliance with the rules, at the request of the Examiner, no fee should be due for this filing, and this filing should not be considered "Applicant Delay" with respect to the Patent Term Adjustment already accrued in this Application. Nevertheless:

**EXCEPT** for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit

Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,  
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**This application is officially maintained in electronic form. To View: Click the desired Document Description. To Download and Print: Check the desired document(s) and click PDF.**

### **Bibliographic Data**

<b>Mail Room Date</b>	<b>Document Code</b>	<b>Document Description</b>	<b>Document Category</b>	<b>Page Count</b>
03-11-2009	NOA	<b>Notice of Allowance and Fees Due (PTOL-85)</b>	PROSECUTION	5
03-11-2009	EXIN	Examiner Interview Summary Record (PTOL - 413)	PROSECUTION	1
03-11-2009	NOA	Notice of Allowance and Fees Due (PTOL-85)	PROSECUTION	3
03-11-2009	IIFW	Issue Information including classification, examiner, name, claim, renumbering, etc.	PROSECUTION	1
03-11-2009	1449	List of References cited by applicant and considered by examiner	PROSECUTION	3
03-11-2009	1449	List of References cited by applicant and considered by examiner	PROSECUTION	1
03-11-2009	SRFW	Search information including classification, databases and other search related notes	PROSECUTION	1
03-11-2009	SRNT	Examiner's search strategy and results	PROSECUTION	15
03-11-2009	SRNT	Examiner's search strategy and results	PROSECUTION	1
03-11-2009	1449	List of References cited by applicant and considered by examiner	PROSECUTION	1
03-11-2009	FWCLM	Index of Claims	PROSECUTION	2
03-11-2009	1449	List of References cited by applicant and considered by examiner	PROSECUTION	1
12-01-2008	WFEE	Fee Worksheet (PTO-875)	PROSECUTION	2
12-01-2008	N417	EFS Acknowledgment Receipt	PROSECUTION	3
12-01-2008	NPL	NPL Documents	PROSECUTION	1
12-01-2008	WFEE	Fee Worksheet (PTO-875)	PROSECUTION	1
12-01-2008	WFEE	Fee Worksheet (PTO-875)	PROSECUTION	1
12-01-2008	TRAN.LET	Transmittal Letter	PROSECUTION	2
12-01-2008	IDS	Information Disclosure Statement (IDS) Filed (SB/08)	PROSECUTION	1
12-01-2008	LET.	Miscellaneous Incoming Letter	PROSECUTION	2
12-01-2008	XT/	Extension of Time	PROSECUTION	1
12-01-2008	ELC.	Response to Election / Restriction Filed	PROSECUTION	1
12-01-2008	CLM	Claims	PROSECUTION	3
12-01-2008	REM	Applicant Arguments/Remarks Made in an Amendment	PROSECUTION	4
09-30-2008	CTRS	Requirement for Restriction/Election	PROSECUTION	4
09-30-2008	FWCLM	Index of Claims	PROSECUTION	1
09-30-2008	BIB	Bibliographic Data Sheet	PROSECUTION	1
01-28-2008	TRAN.LET	Transmittal Letter	PROSECUTION	2
01-28-2008	IDS	Information Disclosure Statement (IDS) Filed (SB/08)	PROSECUTION	1
01-28-2008	FOR	Foreign Reference	PRIOR ART	269
01-28-2008	FOR	Foreign Reference	PRIOR ART	286
01-28-2008	FOR	Foreign Reference	PRIOR ART	99
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07-30-2007	APP.FILE.REC	Filing Receipt	PROSECUTION	3
05-10-2007	CFILE	Request for Corrected Filing Receipt	PROSECUTION	4
04-20-2007	IDS	Information Disclosure Statement (IDS) Filed (SB/08)	PROSECUTION	3
04-20-2007	FOR	Foreign Reference	PRIOR ART	16
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04-20-2007	FOR	Foreign Reference	PRIOR ART	102
04-20-2007	NPL	NPL Documents	PRIOR ART	5
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02-22-2007	NTC.PUB	Notice of Publication	PROSECUTION	1
11-21-2006	APP.FILE.REC	Filing Receipt	PROSECUTION	3
11-21-2006	M903	Notice of DO/EO Acceptance Mailed	PROSECUTION	2
09-07-2006	IDS	Information Disclosure Statement (IDS) Filed (SB/08)	PROSECUTION	8
09-01-2006	IDS	Information Disclosure Statement (IDS) Filed (SB/08)	PROSECUTION	9
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03-15-2006	NPL	NPL Documents	PRIOR ART	18
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03-15-2006	WFEE	Fee Worksheet (PTO-875)	PROSECUTION	1
03-15-2006	WCLM	Claims Worksheet (PTO-2022)	PROSECUTION	1



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A61P 35/00Robert, Hugh [GB/GB]; Alderley Park, Macclesfield,  
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(21) International Application Number: PCT/GB02/04932

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LK, LR, LS, LT, LV, LU, MA, MD, MG, MK, MN, MW,  
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TRAZENECA AB [SE/SE]; S-151 85 Sodertalje (SE).(84) Designated States (regional): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
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GW, ML, MR, NE, SN, TD, TG).(71) Applicant (for MG only): ASTRAZENECA UK LIM-  
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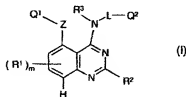
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upon receipt of that reportFor two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: QUINAZOLINE DERIVATIVES AS ANTITUMOR AGENTS



(I)

(57) Abstract: The invention concerns quinazoline derivatives of Formula (I), wherein each of Q<sup>1</sup>, Q<sup>2</sup>, Z, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, L and m have any of the meanings defined in the description; processes for their preparation, pharmaceutical compositions containing them and their use in the manufacture of a medicament for use in the prevention or treatment of tumours which are sensitive to inhibition of erbB receptor tyrosine kinases.

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES  
PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

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(81) Bestimmungsstaaten (national): AE, AG, AL, AM, AT,  
AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR,  
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GH, GM, GR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,  
KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK,  
MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU,  
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CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

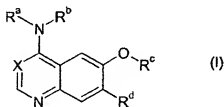
Veröffentlicht:

— mit internationalem Recherchenbericht

Zur Erklärung der Zweibuchstaben-Codes und der anderen Ab-  
kürzungen wird auf die Erklärungen ("Guidance Notes on Co-  
des and Abbreviations") am Anfang jeder regulären Ausgabe der  
PCT-Gazette verwiesen.

(54) Title: 4-(N-PHENYL-AMINO)-QUINAZOLINES / QUINOLINES AS TYROSINE KINASE INHIBITORS

(54) Bezeichnung: 4-(N-PHENYL-AMINO)-CHINAZOLIN/CHINOLIN ALS TYROSINKINASEINHIBITOREN



(57) Abstract: The invention relates to the bicyclic heterocycles of the general formula (I), wherein R<sup>a</sup>, R<sup>b</sup>, R<sup>c</sup>, R<sup>d</sup> and X are defined as in claim 1, the tautomers, stereoisomers, mixtures and salts thereof, especially the physiologically acceptable salts thereof with inorganic or organic acids, which have valuable pharmacological properties, especially an inhibitory effect on tyrosine kinase-mediated signal transduction. The invention also relates to the use of the bicyclic heterocycles in the treatment of diseases, especially cancer diseases and of benign prostate hyperplasia (BPH), of diseases of the lung and the respiratory system, and further to the production of the bicyclic heterocycles.

(57) Zusammenfassung: Die vorliegende Erfindung betrifft bi-  
cyclische Heterocyclen der allgemeinen Formel (I), in der R<sup>a</sup>, R<sup>b</sup>, R<sup>c</sup>, R<sup>d</sup> und X wie im Anspruch 1 definiert sind, deren Tautomere,  
deren Stereoisomere, deren Gemische und deren Salze, insbesondere deren physiologisch verträgliche Salze mit anorganischen oder  
organischen Säuren, welche wertvolle pharmakologische Eigenschaften aufweisen, insbesondere eine Hemmwirkung auf die durch  
Tyrosinkinasen vermittelte Signaltransduktion, deren Verwendung zur Behandlung von Krankheiten, insbesondere von Tumorerkran-  
kungen sowie der benignen Prostatihyperplasie (BPH), von Erkrankungen der Lunge und der Atemwege und deren Herstellung.

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0207323.7 28 March 2002 (28.03.2002) GB  
0230086.1 24 December 2002 (24.12.2002) GB  
0301916.3 28 January 2003 (28.01.2003) GB(71) Applicant (for AE, AG, AL, AM, AT, AU, AZ, BA, BB, BF, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CY, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, FR, GB, GD, GE, GH, GM, GR, HR, HU, ID, IE, IL, IN, IT, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MC, MD, ME, MN, MW, MX, MY, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SZ, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW only): **ASTRAZENECA AB** [SE/SE]; Soderlatje, S-151 85 (SE).(71) Applicant (for MG only): **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London, Greater London W1K 1LN (GB).

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**HENNEQUIN, Laurent, Francois, Andre** [FR/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **KETTLE, Jason, Grant** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).(74) Agent: **ASTRAZENECA**; Global Intellectual Property, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

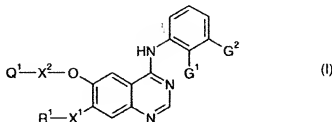
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 4-ANILINO QUINAZOLINE DERIVATIVES AS ANTIPROLIFERATIVE AGENTS

(57) Abstract: The invention concerns quinazoline derivatives of Formulas (I) wherein each of Q<sup>1</sup>, Z, R<sup>1</sup> and Q<sup>2</sup> have any of the meanings defined in the description; processes for their preparation, pharmaceutical compositions containing them and their use in the manufacture of a medicament for use as an antiproliferative agent in the prevention or treatment of tumours which are sensitive to inhibition of erbB receptor tyrosine kinases.



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : <b>C07D 239/94, A61K 31/517</b>		<b>A1</b>	(11) International Publication Number: <b>WO 00/31048</b>
		(43) International Publication Date: 2 June 2000 (02.06.00)	
(21) International Application Number: <b>PCT/US99/22116</b> (22) International Filing Date: <b>23 September 1999 (23.09.99)</b> (30) Priority Data: 60/109,065                      19 November 1998 (19.11.98) <b>US</b> (71) Applicant (for all designated States except US): <b>WARNER-LAMBERT COMPANY [US/US]; 201</b> <b>Tabor Road, Morris Plains, NJ 07950 (US).</b> (72) Inventors; and (75) Inventors/Applicants (for US only): <b>BRIDGES, Alexander,</b> <b>James [GB/US]; 3301 Textile Road, Saline, MI 48176 (US).</b> <b>DRISCOLL, Denise [US/US]; 623 Waymarket Drive, Ann</b> <b>Arbor, MI 48103 (US), KLOHS, Wayne, Daniel [US/US];</b> <b>4559 Sycamore Drive, Ypsilanti, MI 48197 (US).</b> (74) Agents: <b>RYAN, M., Andrea; Warner-Lambert Company, 201</b> <b>Tabor Road, Morris Plains, NJ 07950 (US) et al.</b>		(81) Designated States: <b>AE, AL, AU, BA, BB, BG, BR, CA, CN,</b> <b>CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS,</b> <b>JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX,</b> <b>NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, TZ, UA, US,</b> <b>UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW,</b> <b>SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY,</b> <b>KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH,</b> <b>CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,</b> <b>PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN,</b> <b>GW, ML, MR, NE, SN, TD, TG).</b>  <b>Published</b> <i>With international search report.</i>	
(54) Title: <b>N-[4-(3-CHLORO-4-FLUORO-PHENYLAMINO)-7-(3-MORPHOLIN-4-YL-PROPOXY)-QUINAZOLIN-6-YL]-ACRYLA-</b> <b>MIDE, AN IRREVERSIBLE INHIBITOR OF TYROSINE KINASES</b>			
(57) Abstract  The present invention provides the compound N-[4-(3-chloro -4-fluoro- phenylamino) -7-(3-morpholin -4-yl-propoxy) -quina- zolin-6- yl]-acrylamide that is an irreversible inhibitor of tyrosine kinases. Also provided is a method of treating cancer, restenosis, ath- erosclerosis, endometriosis, and psoriasis using the compound N-[4-(3-chloro -4-fluoro-phenylamino) -7-(3-morpholin -4-yl-propoxy) -quinazolin -6-yl]-acrylamide, and a pharmaceutical composition that contains the compound N-[4-(3-chloro -4-fluoro-phenylamino) -7-(3-morpholin -4-yl-propoxy) -quinazolin-6-yl] -acrylamide.			



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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		(43) International Publication Date: 21 September 2000 (21.09.00)	
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(22) International Filing Date: 14 March 2000 (14.03.00)			
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(71) Applicant (for all designated States except US): BOEHRINGER INGELHEIM PHARMA KG [DE/DE]; D-55216 Ingelheim/Rhein (DE).			
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(74) Agent: LAUDIEN, Dieter; Boehringer Ingelheim GmbH, B Patente, D-55216 Ingelheim/Rhein (DE).		Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: BICYCLIC HETEROCYCLES, PHARMACEUTICAL COMPOSITIONS CONTAINING THESE COMPOUNDS, AND PROCESSES FOR PREPARING THEM			
<p style="text-align: center;">(I)</p>			
(57) Abstract			
<p>The present invention relates to bicyclic heterocyclic compounds of general formula (I), wherein R<sub>a</sub> to R<sub>d</sub>, A to D and X are defined as in claims 1 to 8, the tautomers, stereoisomers and salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases which have valuable pharmacological properties, particularly an inhibitory effect on signal transduction mediated by tyrosine kinases, their use in treating diseases, particularly tumour diseases, diseases of the lung and airways and the preparation thereof.</p>			

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403/12, 401/12, 235/06, A61K 31/505, A61P 35/00Patrick [FR/FR]; Z.I. La Pompelle, Boîte postale 1050,  
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(21) International Application Number: PCT/GB01/02424

(74) Agent: TAIT, Brian, Steele, Astrazeneca, Global Intel-  
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01400565.6 5 March 2001 (05.03.2001) EP(81) Designated States (national): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,  
MX, MY, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,  
SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA,  
ZW.(84) Designated States (regional): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian  
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patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,  
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,  
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).(71) Applicant (for all designated States except MG, US): AS-  
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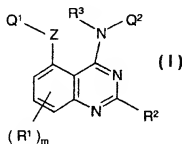
(75) Inventors/Applicants (for US only): HENNEQUIN,  
Laurent, François, André [FR/FR]; Z.I. La Pompelle,  
Boîte Postale 1050, F-51689 Reims Cedex 2 (FR). PLE,

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For two-letter codes and other abbreviations, refer to the "Guide-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: QUINAZOLINE DERIVATIVES FOR THE TREATMENT OF TUMOURS

(57) Abstract: The invention concerns quinazoline derivatives of Formula  
(I) wherein each of Q<sup>1</sup>, Z, m, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and Q<sup>2</sup> have any of the meanings  
defined in the description; processes for their preparation, pharmaceutical  
compositions containing them and their use in the manufacture of a medica-  
ment for use as an anti-invasive agent in the containment and/or treatment  
of solid tumour disease.

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International Bureau

FOR MORE INFORMATION ON PCT, SEE THE PCT HANDBOOK, WHICH IS AVAILABLE FROM THE INTERNATIONAL BUREAU OF PATENT COOPERATION, CHAMBERLIN, GENEVA, SWITZERLAND.

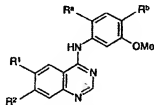
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- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): HENNEQUIN, Laurent, Francois, Andre [FR/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). PLE, Patrick [FR/FR]; Z.I. La Pompelle, BP 1050, F-51689 Reims Cedex 2 (FR).
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- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: QUINAZOLINE DERIVATIVES



(I)

(57) Abstract: The invention concerns quinazoline derivatives of Formula I, wherein each of R<sup>1</sup>, R<sup>2</sup>, R<sup>a</sup> and R<sup>b</sup> have any of the meanings defined in the description; processes for their preparation, pharmaceutical compositions containing them and their use in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

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Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(21) International Application Number: PCT/GB00/04181

(74) Agent: PHILLIPS, Neil, Godfrey, Alasdair; AstraZeneca, Global Intellectual Property, P.O. Box 272,  
Mereside, Alderley Park, Macclesfield, Cheshire SK10  
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HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,  
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,  
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,  
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99402877.7 19 November 1999 (19.11.1999) EP(71) Applicant (for all designated States except MG, US): AS-  
TRAZENECA AB [SE/SE]; S-151 85 Sodertalje (SE).(84) Designated States (regional): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian  
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European  
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,  
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CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).(71) Applicant (for MG only): ASTRAZENECA UK LIM-  
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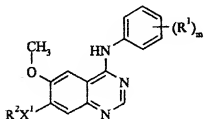
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— With international search report.

For two-letter codes and other abbreviations, refer to the "Guide-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: QUINAZOLINE DERIVATIVES AS VEGF INHIBITORS



(I)

(57) Abstract: The invention relates to quinazoline derivatives of formula (I), wherein m is an integer from 1 to 3; R<sup>1</sup> represents halogeno or C<sub>1-6</sub>alkyl; X<sup>1</sup> represents -O-; R<sup>2</sup> is selected from one of the following three groups: 1) C<sub>1-3</sub>alkylR<sup>3</sup> (wherein R<sup>3</sup> is piperidin-4-yl which may bear one or two substituents selected from hydroxy, halogeno, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>hydroxyalkyl and C<sub>1-6</sub>alkoxy; 2) C<sub>2-3</sub>alkenylR<sup>3</sup> (wherein R<sup>3</sup> is as defined hereinbefore); 3) C<sub>2-3</sub>alkynylR<sup>3</sup> (wherein R<sup>3</sup> is as defined hereinbefore); and wherein any alkyl, alkenyl or alkynyl group may bear one or more substituents selected from hydroxy, halogeno and amino; and salts thereof; processes for their preparation, pharmaceutical compositions containing a compound of formula (I) or a

pharmaceutically acceptable salt thereof as active ingredient. The compounds of formula (I) and the pharmaceutically acceptable salts thereof inhibit the effects of VEGF, a property of value in the treatment of a number of disease states including cancer and rheumatoid arthritis.



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			Applicants: <b>HENNEQUIN et al.</b>			
			Filing Date: <b>March 15, 2006</b>		Group Art Unit: <b>Unassigned</b>	
<b>U.S. PATENT DOCUMENTS</b>						
Initial	Document No.	Date	Name	Class	Sub-Class	Filing Date
1.	US 20020049197	April 25, 2002	Himmelsbach et al.	514	217.06	August 23, 2001
2.	US 20020082270	June 27, 2002	Himmelsbach et al.	514	266.2	August 22, 2001
3.	US 20020082271	June 27, 2002	Himmelsbach et al.	514	266.24	August 22, 2001
4.	US 20020128553	September 12, 2002	Mishani et al.	600	431	March 12, 2001
5.	US 20020169180	November 14, 2002	Himmelsbach et al.	514	266.4	December 10, 2001
6.	US 20020173509	November 21, 2002	Himmelsbach et al.	514	234.5	December 17, 2001
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10.	US 20030225079	December 4, 2003	Singer et al.	514	233.8	May 8, 2003
11.	US 20040044014	March 4, 2004	Himmelsbach et al.	514	266.4	April 17, 2003
12.	US 20040048880	March 11, 2004	Himmelsbach et al.	514	266.2	March 27, 2003
13.	US 20040176361	September 9, 2004	Fujio et al.	514	224.2	February 24, 2004
14.	US 20050148607	July 7, 2005	Suzuki et al.	514	264.11	June 3, 2003
15.	US 20050165035	July 28, 2005	Bradbury et al.	514	266.22	June 1, 2004
16.	US 3,812,257	May 21, 1974	Yamamoto	514	266.21	April 7, 1972
17.	US 3,971,783	July 27, 1976	Barnish et al.	514	284	April 26, 1974
18.	US 4,335,127	June 15, 1982	Vandenberk et al.	514	266.22	October 12, 1979
19.	US 4,921,863	May 1, 1990	Sugimoto et al.	514	319	February 17, 1988
20.	US 5,411,963	May 2, 1995	Dreikorn et al.	514	266.3	July 19, 1993
21.	US 5,457,105	October 10, 1995	Barker	514	234.5	August 2, 1994
22.	US 5,616,582	April 1, 1997	Barker	514	234.5	June 15, 1995
23.	US 5,747,498	May 5, 1998	Schnur et al.	514	266.4	May 28, 1996
24.	US 5,770,599	June 23, 1998	Gibson	514	224.2	April 26, 1996
25.	US 5,817,678	October 6, 1998	Kim et al.	514	326	November 15, 1996
26.	US 6,127,366	October 3, 2000	Kim et al.	514	235.5	October 5, 1998
27.	US 6,177,433	January 23, 2001	Uckun et al.	514	266.4	November 19, 1999
28.	US 6,200,976	March 13, 2001	Ries et al.	514	249	March 29, 1999
29.	US 6,297,258	October 2, 2001	Wissner et al.	514	319	August 1, 2000
30.	US 6,313,127	November 6, 2001	Waterson et al.	514	253.01	July 31, 1998
31.	US 6,541,491	April 1, 2003	Davies et al.	514	340	November 30, 2000
32.	US 6,562,319	May 13, 2003	Mishani et al.	424	1.81	March 12, 2001
33.	US 6,617,329	September 9, 2003	Himmelsbach et al.	514	252.14	August 23, 2001
34.	US 6,653,305	November 25, 2003	Himmelsbach et al.	514	234.5	August 15, 2001
<b>FOREIGN PATENT DOCUMENTS</b>						
	Document No.	Date	Country	Class	Sub-Class	Translation
<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, etc.)</b>						
Examiner						
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<b>INFORMATION DISCLOSURE CITATION</b> (Use several sheets if necessary)		Attorney Docket No. <b>056291-5241</b>	Application No. <b>10/573,090</b>	
<b>RESUBMISSION OF</b> <b>PTO Form 1449</b> <b>September 1, 2006</b>		Applicants: <b>HENNEQUIN et al.</b>		
		Filing Date: <b>March 15, 2006</b>	Group Art Unit: <b>Unassigned</b>	

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35.	US 6,656,946	December 2, 2003	Himmelsbach et al.	514	266.4	August 22, 2001
36.	US 6,740,651	May 25, 2004	Himmelsbach et al.	514	228.8	August 22, 2001
37.	US 6,972,288	December 6, 2005	Himmelsbach et al.	514	234.8	February 6, 2002

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38.	DE 19908567	August 31, 2000	Germany	Boehringer Ingelheim Pharma KG	US 6,972,288	
39.	EP 0 288 563	May 11, 1994	EPO	Eisai Co., Ltd.		
40.	EP 0 566 226	November 8, 1995	EPO	Zeneca Limited		
41.	EP 0 585 371	April 17, 2002	EPO	Rhone-Poulenc Rorer Int.(Holdings) Inc.		
42.	EP 0 669 324	August 30, 1995	EPO	Eisai Co., Ltd.		
43.	EP 0 837 063	April 22, 1998	EPO	Pfizer Inc.		
44.	EP 1 044 969	October 18, 2000	EPO	Pfizer Products Inc.		
45.	EP 1 230 919	August 14, 2002	EPO	Warner-Lambert Company		
46.	EP 1 369 418	December 10, 2003	EPO	Mitsubishi Pharma Corporation		
47.	EP 1 548 008	June 29, 2005	EPO	Kirin Beer Kabushiki Kaisha		
48.	GB 2,295,387	May 29, 1996	United Kingdom	Glaxo Inc.		
49.	WO 88/02365	April 7, 1988	WIPO	EISAI Co., Ltd. Et al.	US 4,921,863	
50.	WO 92/20642	November 26, 1992	WIPO	Rhone-Poulenc Rorer Int.(Holdings) Inc.		
51.	WO 95/00146	January 5, 1995	WIPO	Rhone-Poulenc Rorer Pharm. Inc.		
52.	WO 95/15758	June 15, 1995	WIPO	Rhone-Poulenc Rorer Pharma. Inc.		
53.	WO 96/09294	March 28, 1996	WIPO	The Wellcome Foundation Limited		
54.	WO 96/30347	October 3, 1996	WIPO	Pfizer Inc.		
55.	WO 96/33977	October 31, 1996	WIPO	Zeneca Limited		
56.	WO 96/33978	October 31, 1996	WIPO	Zeneca Limited		
57.	WO 96/33978	October 31, 1996	WIPO	Zeneca Limited		
58.	WO 96/33980	October 31, 1996	WIPO	Zeneca Limited		
59.	WO 96/33981	October 31, 1996	WIPO	Zeneca Limited		
60.	WO 96/39145	December 12, 1996	WIPO	Rhone-Poulenc Rorer Pharma. Inc.		
61.	WO 97/03069	January 30, 1997	WIPO	Glaxo Group Limited		
62.	WO 97/06138	February 20, 1997	WIPO	Zeneca Limited		
63.	WO 97/18813	May 29, 1997	WIPO	Merck & Co., Inc.		
64.	WO 97/22596	June 26, 1997	WIPO	Zeneca Limited et al.		
65.	WO 97/28128	August 7, 1997	WIPO	Zeneca Limited		
66.	WO 97/30034	August 21, 1997	WIPO	Zeneca Limited		
67.	WO 97/30035	August 21, 1997	WIPO	Zeneca Limited et al.		
68.	WO 97/30044	August 21, 1997	WIPO	Zeneca Limited		

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69.	WO 97/32856	September 12, 1997	WIPO	Zeneca Limited et al.	
70.	WO 97/38983	October 23, 1997	WIPO	Warner-Lambert Company	
71.	WO 97/38943	October 23, 1997	WIPO	Zeneca Limited	
72.	WO 98/02434	January 22, 1998	WIPO	Glaxo Group Limited	
73.	WO 98/13354	April 2, 1998	WIPO	Zeneca Limited et al.	
74.	WO 98/38984	September 11, 1998	WIPO	Sugen Inc.	
75.	WO 99/06378	February 11, 1999	WIPO	Warner-Lambert Company	
76.	WO 99/35132	July 15, 1999	WIPO	Glaxo Group Limited	
77.	WO 99/54313	October 28, 1999	WIPO	Boehringer Ingelheim Pharma KG	US 6,200,976
78.	WO 00/10981	March 2, 2000	WIPO	Parker Hughes Institute	
79.	WO 00/12497	March 9, 2000	WIPO	Scios Inc.	
80.	WO 00/18740	April 6, 2000	WIPO	American Cyanamid Company	
81.	WO 00/20402	April 13, 2000	WIPO	Zeneca Limited	
82.	WO 00/21955	April 20, 2000	WIPO	Zeneca Limited et al.	
83.	WO 00/24718	May 4, 2000	WIPO	Akzo Nobel N.V.	
84.	WO 00/31048	June 2, 2000	WIPO	Warner-Lambert Company	
85.	WO 00/44728	August 3, 2000	WIPO	Pfizer Products Inc.	
86.	WO 00/47212	August 17, 2000	WIPO	Zeneca-Pharma S.A.	
87.	WO 00/51991	September 8, 2000	WIPO	Boehringer Ingelheim Pharma KG	
88.	WO 00/55141	September 21, 2000	WIPO	Boehringer Ingelheim Pharma KG	
89.	WO 00/56720	September 28, 2000	WIPO	Parker Hughes Institute	
90.	WO 00/78735	December 28, 2000	WIPO	Boehringer Ingelheim Pharma KG	US 20020169180
91.	WO 01/07432	February 1, 2001	WIPO	SmithKline Beecham PLC	
92.	WO 01/19788	March 22, 2001	WIPO	Cor Therapeutics Inc.	
93.	WO 01/21594	March 29, 2001	WIPO	AstraZeneca AB et al.	
94.	WO 01/21595	March 29, 2001	WIPO	AstraZeneca AB et al.	
95.	WO 01/21596	March 29, 2001	WIPO	AstraZeneca AB et al.	
96.	WO 01/21597	March 29, 2001	WIPO	AstraZeneca AB et al.	
97.	WO 01/32651	May 10, 2001	WIPO	AstraZeneca AB et al.	
98.	WO 01/77085	October 18, 2001	WIPO	AstraZeneca AB et al.	
99.	WO 01/94341	December 13, 2001	WIPO	AstraZeneca AB et al.	
100.	WO 01/98277	December 27, 2001	WIPO	Pfizer Products Inc.	
101.	WO 02/16352	February 28, 2002	WIPO	AstraZeneca AB et al.	
102.	WO 02/18351	March 7, 2002	WIPO	Boehringer Ingelheim Pharma KG	US 20020082271

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103.	WO 02/18370	March 7, 2002	WIPO	Boehringer Ingelheim Pharma KG	US 20020082270
104.	WO 02/18372	March 7, 2002	WIPO	Boehringer Ingelheim Pharma KG	US 6,617,329
105.	WO 02/18373	March 7, 2002	WIPO	Boehringer Ingelheim Pharma KG	US 6,653,305
106.	WO 02/18376	March 7, 2002	WIPO	Boehringer Ingelheim Pharma KG	US 6,740,651
107.	WO 02/24684	March 28, 2002	WIPO	SmithKline Beecham PLC	
108.	WO 02/30924	April 18, 2002	WIPO	AstraZeneca AB et al.	
109.	WO 02/34744	May 2, 2002	WIPO	AstraZeneca AB et al.	
110.	WO 02/41882	May 30, 2002	WIPO	Novartis AG et al.	
111.	WO 02/44166	June 6, 2002	WIPO	AstraZeneca AB et al.	
112.	WO 02/48117	June 20, 2002	WIPO	Fujisawa Pharmaceutical Co., Ltd.	
113.	WO 02/50043	June 27, 2002	WIPO	Boehringer Ingelheim Pharma KG	US 20020173509
114.	WO 02/056882	July 25, 2002	WIPO	SmithKline Beecham PLC	
115.	WO 02/066445	August 29, 2002	WIPO	Mitsubishi Pharma Corporation	EP 1 369 418
116.	WO 02/068409	September 6, 2002	WIPO	Merck & Co. Inc.	
117.	WO 02/073235	September 19, 2002	WIPO	Yissum Research Development et al.	
118.	WO 02/076976	October 3, 2002	WIPO	Bayer Corporation	
119.	WO 02/092577	November 21, 2002	WIPO	AstraZeneca AB et al.	
120.	WO 02/092578	November 21, 2002	WIPO	AstraZeneca AB et al.	
121.	WO 02/097490	December 5, 2002	WIPO	LnI Technologies Canada Inc.	
122.	WO 02/102315	December 27, 2002	WIPO	Bristol-Myers Squibb Company	
123.	WO 03/060188	January 3, 2003	WIPO	Ariad Pharmaceuticals Inc.	
124.	WO 03/031406	April 17, 2003	WIPO	IRM LLC	
125.	WO 03/040108	May 15, 2003	WIPO	AstraZeneca AB et al.	
126.	WO 03/040102	May 15, 2003	WIPO	AstraZeneca AB et al.	
127.	WO 03/045364	June 5, 2003	WIPO	AstraZeneca AB et al.	
128.	WO 03/045395	June 5, 2003	WIPO	AstraZeneca AB et al.	
129.	WO 03/049740	June 19, 2003	WIPO	Pfizer Products Inc.	
130.	WO 03/066060	August 14, 2003	WIPO	Boehringer Ingelheim Pharma GmbH...	US 20030149062
131.	WO 03/068264	August 21, 2003	WIPO	Boehringer Ingelheim Pharma GmbH...	US 20030158196
132.	WO 03/082290	October 9, 2003	WIPO	Boehringer Ingelheim Pharma GmbH...	US 20040048880
133.	WO 03/082831	October 9, 2003	WIPO	Boehringer Ingelheim Pharma GmbH...	
134.	WO 03/089439	October 30, 2003	WIPO	Boehringer Ingelheim Pharma GmbH...	US 20040044014
135.	WO 03/094921	November 20, 2003	WIPO	Boehringer Ingelheim Pharma GmbH...	US 20030225079
136.	WO 03/099276	December 4, 2003	WIPO	Bristol-Myers Squibb Company	

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<b>RESUBMISSION OF</b> <b>PFO Form 1449</b> <b>September 1, 2006</b>				Applicants: <b>HENNEQUIN et al.</b>			
				Filing Date: <b>March 15, 2006</b>		Group Art Unit: <b>Unassigned</b>	

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137.	WO 03/101491	December 11, 2003	WIPO	Mitsubishi Pharma Corporation	US 20050148607	
138.	WO 2004/006846	January 22, 2004	WIPO	Exelixis Inc.		
139.	WO 2004/064718	August 5, 2004	WIPO	T.K. Signal Ltd.		
140.	WO 2004/096226	November 11, 2004	WIPO	AstraZeneca AB et al.		
141.	WO 2005/013998	February 17, 2005	WIPO	AstraZeneca AB et al.		
142.	WO 2005/026156	March 24, 2005	WIPO	AstraZeneca AB et al.		
143.	WO 2005/026157	March 24, 2005	WIPO	AstraZeneca AB et al.		
144.	WO 2005/030757	April 7, 2005	WIPO	AstraZeneca AB et al.		
145.	WO 2005/030765	April 7, 2005	WIPO	AstraZeneca AB et al.		
146.	WO 2005/075439	August 18, 2005	WIPO	AstraZeneca AB et al.		

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147.	Gaul et al. "Discovery and Biological Evaluation of Potent Dual ErbB-2/EGFR tyrosine Kinase Inhibitors: 6-thiazolylquinazolines" Bioorganic & Medicinal Chemistry Letters 13: 637-640 (2003)
148.	Hennequin et al. "Design and structure-activity relationship of a new class of potent VEGF receptor tyrosine kinase inhibitors" Journal Of Medicinal Chemistry 42:5369-5389 (1999)
149.	Hennequin et al. "Novel 4-anilinoquinazolines with C-7 basic side chains : Design and structure activity relationship of a series of potent, orally active, VEGF receptor tyrosine kinase inhibitors" Journal Of Medicinal Chemistry 45(6):1300-1312 (2002)
150.	Smaill et al. "Tyrosine kinase Inhibitors. 17. Irreversible Inhibitors of the Epidermal Growth Factor Receptor: 4-(phenylamino)quinazolin- and 4-(phenylamino)pyrido[3,2-d]pyrimidine-6-acrylamides bearing additional solubilizing function" Journal of Medicinal Chemistry 43(7):1380-1397 (2000)
151.	Stamos et al. "Structure of the Epidermal Growth Factor Receptor Kinase Domain Alone and in Complex with a 4-Anilinoquinazoline Inhibitor" J. Biol. Chem. 277(48):46265-46272 (2002)
152.	Traxler et al. "Protein tyrosine kinase inhibitors in cancer treatment" Exp. Opin. Ther. Patents 7(6):571-588 (1997)
153.	Traxler et al. "Tyrosine kinase inhibitors in cancer treatment (Part II)" Exp. Opin. Ther. Patents 8(12):1599-1625 (1998)
154.	Isou et al. "6-Substituted-4-(3-bromophenylamino)quinazolines as Putative Irreversible Inhibitors of the Epidermal Growth Factor Receptor (EGFR) and Human Epidermal Growth Factor Receptor (HER-2) Tyrosine Kinases with Enhanced Antitumor Activity" J. Med. Chem. 44:2719-2734 (2001)
155.	Vema et al. "Design of EGFR kinase inhibitors: a ligand-based approach and its confirmation with structure-based studies" Bioorg Med Chem. 11(21):4643-4653 (2003)

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